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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/260,037 03/02/99 YACOBY-ZEEVI

0 910/13

EXAMINER

HM22/0409

SOL SHEINBEIN  
G.E. EHRLICH (1995) LTD.  
2001 JEFFERSON DAVIS HIGHWAY  
SUITE 207  
ARLINGTON VA 22202

HUTSON, R	
ART UNIT	PAPER NUMBER

1652  
DATE MAILED:

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04/09/01

**Please find below and/or attached an Office communication concerning this application or proceeding.**

**Commissioner of Patents and Trademarks**

# Office Action Summary

Application No.  
**09/260,037**

Applicant(s)  
**Yacoby-Zeevi**

Examiner  
**Richard Hutson**

Group Art Unit  
**1652**



☒ Responsive to communication(s) filed on Jan 30, 2001

☐ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1035 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

## Disposition of Claim

☒ Claim(s) 54-57 and 59 is/are pending in the applicat

Of the above, claim(s) \_\_\_\_\_ is/are withdrawn from consideration

☐ Claim(s) \_\_\_\_\_ is/are allowed.

☒ Claim(s) 54-57 and 59 is/are rejected.

☐ Claim(s) \_\_\_\_\_ is/are objected to.

☐ Claims \_\_\_\_\_ are subject to restriction or election requirement.

## Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on \_\_\_\_\_ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on \_\_\_\_\_ is ☐ approved ☐ disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some\* ☒ None of the CERTIFIED copies of the priority documents have been  
☐ received.

☐ received in Application No. (Series Code/Serial Number) \_\_\_\_\_.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

\*Certified copies not received: \_\_\_\_\_

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

## Attachment(s)

☐ Notice of References Cited, PTO-892

☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). \_\_\_\_\_

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

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## **DETAILED ACTION**

### ***Continued Prosecution Application***

1. The request filed on 1/30/2001 for a Continued Prosecution Application (CPA) under 37 CFR 1.53(d) based on parent Application No. 09/260,037 is acceptable and a CPA has been established. An action on the CPA follows.

Applicants cancellation of claims 1-53 and the addition of claims 54-59 in Amendment B, Paper No: 12, filed 11/29/2000 followed by applicants cancellation of claim 58 and amendment of claims 54 and 57 in Amendment C, paper No: 17, filed on 1/30/2001 is acknowledged. Claims 54-57 and 59 are at issue and are present for examination.

Applicants' arguments filed on 11/29/2000, paper No. 12, have been fully considered and are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

### ***Claim Rejections - 35 USC § 112***

2. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

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3. Claims 54-57 and 59 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 54-57 and 59 are indefinite in the recitation of "a purified, natural or recombinant, glycosaminoglycan degrading enzyme" in that it is unclear if applicants intent is to a "purified natural or purified recombinant glycosaminoglycan degrading enzyme" or to a "a purified, natural, or recombinant glycosaminoglycan degrading enzyme". For the purpose of examination, the recitation has been interpreted as the second, broader of the two interpretations, "a purified, natural, or recombinant glycosaminoglycan degrading enzyme".

4. Claims 54-57 and 59 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a biological preparation comprising ex vivo, cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and a natural or recombinant purified heparanase being externally adhered thereto, does not reasonably provide enablement for a biological preparation comprising ex vivo, a cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and any natural or recombinant purified glycosaminoglycan degrading enzyme being externally adhered thereto. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

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Claims 54-57 and 59 are so broad as to encompass a biological preparation comprising ex vivo, a cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and **any natural or recombinant purified glycosaminoglycan degrading enzyme** being externally adhered thereto. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of glycosaminoglycan degrading enzymes broadly encompassed by the claims. Since the specific functional properties of the glycosaminoglycan degrading enzyme adhered to said cells or tissue determines the effectiveness of utility of said biological preparation, predictability of those enzymes that may be adhered to said cells or tissue and result in the desired activity requires a detailed knowledge of said glycosaminoglycan degrading enzymes and how the specific enzyme used relates to intended biological function of the preparation. However, in this case the disclosure is limited to a biological preparation comprising ex vivo, cells in suspension or a tissue selected from the group consisting of an embryo, a skin graft and a nerve, and any natural or recombinant purified heparanase enzyme being externally adhered thereto.

The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the utility of the biological preparation comprising ex vivo, any cells in suspension or a tissue portion and any natural or recombinant purified glycosaminoglycan degrading enzyme being externally adhered thereto, encompassed by the claims. It would require undue experimentation of the skilled artisan to use any of the claimed biological preparation comprising ex vivo, any natural or recombinant purified glycosaminoglycan degrading enzyme

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being externally adhered thereto. The specification is limited to teaching use of the glycosaminoglycan degrading enzyme, heparanase and provides no guidance with regard to other glycosaminoglycan degrading enzymes which may also be used. In view of the great breadth of the claims, amount of experimentation required to make the claimed biological preparation, the lack of guidance, working examples, and unpredictability of the art in predicting which glycosaminoglycan degrading enzymes would be useful, the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the biological preparations encompassed by this claim.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including any biological preparation comprising ex vivo, any cells in suspension or a tissue portion selected from the group consisting of an embryo, a skin graft and a nerve, and any purified, natural or recombinant, glycosaminoglycan degrading enzyme being externally adhered thereto. The scope of the claims must bear a reasonable correlation with the scope of enablement (In re Fisher, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

***Claim Rejections - 35 USC § 102***

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5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 54 and 56 are rejected under 35 U.S.C. 102(b) as being anticipated by Bartlett et al.

Bartlett et al. teach a comparative analysis of the ability of leucocytes, endothelial cells and platelets to degrade the subendothelial basement membrane. Bartlett et al. specifically teach preparation of human platelets from venous blood and resuspended in RPMI-1640 medium containing 10% FCS. Bartlett et al. further teach that both platelets and endothelial cells in suspension expressed heparanase and each of these cell suspensions were able to degrade the extracellular matrix in an extracellular matrix assay, thus these enzymes are adhered to these cells such that they are able to degrade this extracellular matrix. Further, Bartlett et al. teach that expression of such enzymes is necessary for the adhesion, extravasation and movement of these cells through the blood vessel wall prior to entry into inflammatory sites. Applicant is reminded that as discussed in previous office actions, applicants amendment of claims to recite "for use in vivo" and "so as to enhance extravasation... of said cells in vivo", are intended "uses" of the biological preparation therefore carry no patentable weight.

***Claim Rejections - 35 USC § 103***

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The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 57 and 59 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fuks et al. (US Pat No: 5,362,641), Wang et al. (J. Orthop. Res., 14 (2): 149-153 1996, abstract) and Myers et al. (Am J. Surg. 170(1): 75-83, 1995 Jul).

Fuks et al. teach a substantially purified heparanase from human SK-HEP-1 cell line and a method to purify the heparanase. They teach the use of this heparanase as the basis for a pharmaceutical composition comprising the heparanase in combination with a pharmaceutically acceptable, preferably slow releasing carrier (column 5, lines 17-30). Such a composition is useful for the treatment of wounds and enhancement of the wound-healing process. Fuks et al. further teach that the extracellular matrix appears to be essential to the control of cell proliferation and morphogenesis and that heparan sulfate proteoglycans (HSPG), as a principal component of basement membranes plays a integral role in tissue architecture and function. A number of normal and abnormal physiological conditions and disorders are associated with the degradation of the extracellular matrix of various tissues, such as neutrophil mobilization during the inflammatory process as well as tumor cell invasion during metastasis. Thus the invading cells must be capable of producing ECM degrading enzymes in order to move through the tissue.



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The enzymes include in addition to heparanase, chondroitinase, hyaluronidase and keratanase as well as other ECM degrading enzymes.

Fuks et al. teach in addition to the above function ECM degradation an additional function of heparanase is the release of growth factors from basement membranes and subendothelial ECM such as angiogenic, endothelial (ECGF) and fibroblast growth factors (FGF). FGF is essential in the proliferation of fibroblasts and virtually all other mesoderm and neuro-ectoderm-derived cells which are responsible for the production of collagen tissue. Fuks et al. teach that FGF is stored within the basement membrane and bound to heparan sulfate until an exogenous factor such as heparanase causes its release. Fuks et al. teach that heparanase may provide an effective method to mobilize and activate the ECM-bound FGF and hence promote the wound healing process as well as other pathological conditions which are likely to benefit from neovascularization promoted by FGF including cardiac, cerebral and peripheral ischaemic diseases associated with vascular damage. Other potential clinical applications for angiogenic factors taught by Fuks et al. are in processes such as ovulation, hair growth, transplantation, nerve regeneration and bone and cartilage repair.

Wang et al. teach that basic fibroblast growth factor enhances bone-graft incorporation. Specifically Wang et al. teach the implantation of bone grafts, which had been previously soaked overnight in basic fibroblast growth factor, into the proximal tibiae of recipient rats.

Myers et al. teach the transplantation of keratinocytes in the treatment of wounds.

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Myers et al. teach that keratinocyte grafting can be used to treat acute traumatic and chronic non-healing wounds and the keratinocyte sheets secrete many growth factors which have effects on wound healing apart from the “take” of the keratinocyte sheet. Myers et al. show that pretreatment of the wound bed with viable dermis greatly increases the take of keratinocyte grafts.

One of ordinary skill in the art at the time of filing would have been motivated to pretreat keratinocyte grafts prior to implantation of the grafts in recipient tissue with a growth factor or other factor to stimulate integration of the graft into the recipient tissue. Such pretreatment of tissue prior to its transplantation is taught by Wang et al. Based on the teaching of Fuks et al. one of ordinary skill in the art at the time of filing would have been motivated to treat said keratinocyte grafts with heparanase as opposed to a specific growth factor in order to stimulate the release of endogenous growth factors such as FGF from the recipient tissue. As taught by Fuks et al., the use of heparanase to release FGF from its natural setting has the advantage of the cells responding locally to the endogenous natural growth factors and appropriate amount as opposed to high doses of FGF which have been shown to be toxic to various cell types including endothelial cells. Further Fuks et al. teach that heparanase has other beneficial effects on the wound healing process such as the breakdown of the ECM, a necessary part of the integration of invading or transplanted cells.

Therefore, claims 57 and 59 are made obvious by Fuks et al., Wang et al. and Myers et al.


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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on M-F from 7:30 to 4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy (Murthy), can be reached on (703) 308-3804. The fax number for Official Papers to Technology Center 1600 is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson Ph.D.  
3/30/2001

  
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